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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/673,302	Applicant(s) LAW ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 1/2/022, Paper No. 6, has been entered. Claims 1-68 have been amended.

Claims 1-68 are pending and being examined on the merits.

Any rejection made of record in the prior Office action, mailed 8/2/01, Paper No. 5, and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

Priority

Applicants' Amendment to the specification is proper and has been entered, as the Amendment provides references to prior co-pending application(s).

Claim Rejections - 35 USC § 101

The rejection of claims 1-24 under 35 U.S.C. 101 is withdrawn in view of Applicants' amendment(s) to the claims.

Specification

The amendment filed 1/2/02, Paper No. 6, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amendment is directed to the generation of the murine genomic sequence of GP

IIIa, and incorporates by reference, Lanza *et al.*, however, Lanza *et al.* is not provided, nor is it particularly shown where Lanza *et al.* teach the subject matter to be referenced. The Amendment states that, "Therefore, several PCR primers were generated towards the mouse GP IIIa sequence in areas, which, in the case of human GP IIIa (SEQ ID NO: 1), spanned the two exons known to encode the cytoplasmic domain of GP IIIa, i.e., exons M and N. [Lanza, F. *et al.* (1990) *J. Biol. Chem.* 265:18098-18103]." The attempt to incorporate subject matter into this application by reference to Lanza *et al.* is improper because Applicants have not provided Lanza *et al.*, nor have Applicants specifically pointed to where in Lanza *et al.* the subject matter being incorporated may be found. MPEP 608.01(p) states, "Mere reference to another application, patent or publication is not an incorporation of anything therein into the application containing such references for the purpose of the disclosure required by 35 U.S.C. 112, 1st paragraph. In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found."

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 9, 15, 21, 27, 32, 39, 44, 53, 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that, "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

To the extent that the claimed transgenic non-human mammals and/or methods are not described in the instant disclosure, claims 3, 9, 15, 21, 27, 32, 39, 44, 53, 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement." *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981). MPEP 2163.02 teaches that, "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those

skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes, "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not new matter is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure* (emphasis added).

Applicants' Amendment states that PCR primers were generated towards the mouse GP IIIa sequence, and then provides the human GP IIIa amino acid sequence (SEQ ID NO: 1). It is not clear how PCR primers could be generated from an amino acid sequence. Nor is it clear if SEQ ID NO: 1 refers to the entire human GP IIIa sequence, or the two exons, M and N. Therefore, even if the amendment were proper, there would still be no support in the specification of specific primers needed to generate the mouse GPIIIa sequence. An amino acid sequence does not lead to specific primers such that possession at the time of filing would have been conveyed to the skilled artisan.

Accordingly, the claimed invention is rejected as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described

The prior rejection of claims 1-68 under 35 U.S.C. 112, first paragraph, is maintained, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the specification provides adequate written description of the claimed invention. Applicants state that the specification has been amended to include the entire amino acid sequence of SEQ ID NO: 1, which clearly shows multiple tyrosine residues available for phosphorylation, including residues 747 and 759. Applicants state that this sequence has been incorporated by reference to Lanza *et al.*, and thus, specific written description is now provided for residues 747 and 759 and for the cytoplasmic domain of GP IIIa, and that in light of the highly conserved nature of the gene, one of ordinary skill would find adequate guidance and written description to practice the invention across the full scope of the invention as claimed [see p. 20, 1st paragraph of Applicants' Response].

Applicants' arguments have been considered, however, they are not found persuasive. As stated by Applicants, "written description is now provided for residues 747 and 759" [see p. 20, 1st paragraph lines 6-7 of Applicants' Response]. The Examiner agrees that written description is provided for residues 747 and 759;

however, the prior written description rejection of the instant invention is directed to the fact that the only described mutant murine GP IIIa gene, where at least one of the two cytoplasmic tyrosine residues (747 and 759) has been replaced with a phenylalanine residue, meet the written description provision of 35 U.S.C. § 112. Simply stating that there would be "multiple tyrosine residues available for phosphorylation" does not provide adequate written description for the breadth of the claims, directed to any mutant GP IIIa gene where at least one of the two cytoplasmic tyrosine residues encoded by the gene has been replaced with any non-tyrosine residue lacks a written description. The specification does not teach or suggest the replacement of other tyrosine residues [aside from 747 and 759] to produce a mutant murine GP IIIa gene. Specifically, the specification teaches that the phosphorylation of two tyrosine residues at positions 747 and 759 are important for normal integrin /cytoskeletal interactions [see pp. 4-5 of the specification]. Applicants' statement that there would be "multiple tyrosine residues" available for phosphorylation does not provide written description for the broadly claimed mutant murine GP IIIa gene. Furthermore, the specification fails to describe any other mutant GP IIIa genes which could be constructed and used as claimed. The skilled artisan cannot envision all such mutant GP IIIa genes, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)

and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

The prior rejection of claims 1-68 under 35 U.S.C. 112, first paragraph, is maintained, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to a non-human mammal and methods of making a non-human mammal expressing a transgene stably introduced into its DNA, wherein the transgene comprises a mutant GP IIIa where at least one or more phosphorylable cytoplasmic domain tyrosine residues has been replaced with a non-tyrosine residue and methods of using the same.

Applicants argue that, contrary to the position of the Office, the phenotype of the claimed non-human mammals is disclosed on p. 18, lines 15-18, wherein it is disclosed that normal platelet aggregation is dependent on phosphorylation, and that the transgenic mammals of the present invention will display non-normal platelet aggregation. Applicants present Exhibit A [Law *et al.*]as further support for this phenotype.

Applicants' arguments and Exhibit A, Law *et al.,* have been carefully considered, however, they are not found fully persuasive. Law *et al.* teach that mice that express an αIIbβ3 transgene where the tyrosine residues have been mutated to phenylalanines, and it was found that these mice have defective aggregation and

clot-retraction responses *in vitro*, and an *in vivo* bleeding defect, which is pronounced by the tendency to rebleed [see *Abstract*]. However, it is noted that the described mice of Exhibit A do not contain the same transgene and promoter as the instant invention. As stated in the prior Office action, the phenotype observed in any transgenic mouse is directly influenced by the transgene and promoter used. In the instant case, Law *et al.* used an αIIbβ3 transgene, which is a different protein-protein interaction than the claimed GPIIIa which, is a resultant of β3 interaction. The specification teaches that integrins [such as αIIb and β3] play a role in many biological responses, as well as participating in signal transduction. For example aV and β3 pairing mediates diverse biological processes, such as bone resorption, angiogenesis, etc. [see pp. 2-5 of the specification]. With such diverse functions, the specification does not provide sufficient guidance that would lead the skilled artisan to the conclusion that the mutant GP IIIa transgene would produce non-normal platelet aggregation in the described transgenic mice. Furthermore, it is noted that the phenotype of non-normal platelet aggregation that Applicants point to is not supported by the results presented in the Examples. In particular, Example 5, which discusses the generation of mutant mice, the specification states, "The mutant animals are viable and express GP IIb-IIIa on their platelets at similar levels to those seen in normal animals expressing non-mutant GP-IIIa when the platelets are stained with an anti-GP IIb-IIIa antibody and examined on the FACS." [See p. 22, lines 9-12]. The specification does not provide a particular phenotype associated with the claimed mutant mice, as the specification teaches that the

transgenic mice express GP IIIa in levels that are comparable to those in normal mice [not non-normal platelet aggregation]. There is no teaching or guidance provided by the specification to show that the transgenic mice have non-normal platelet aggregation.

Applicants argue that, contrary to the position of the Office, the claims do not claim any particular level of expression. Furthermore, Applicants argue that the interrelationship of GP IIIa protein phosphorylation with numerous cellular responses has been established, and it is asserted that GP IIIa expression, despite species variation, would result in a discernible phenotype [see p. 21, 3rd paragraph of the Response].

In response, it is noted that the claims as written broadly read on any transgenic non-human mammals, which, for reasons advanced in the previous Office action, the specification has not provided an enabling disclosure for [see pp. 6-12]. In particular, the state of the art of transgenics is such that a desired phenotype cannot be achieved by simply introducing transgene constructs of the types recited in the claims. This is because the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype . While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic non-human mammals comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic

animal are directly dependent on the specific transgene construct. Furthermore, species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Although Applicants point to a relationship between GP IIIa protein phosphorylation with numerous cellular responses has been established, there is no evidence, teachings or guidance provided by the specification to show that introducing the transgene as described, into any particular species of mammal, would produce a desired phenotype. Further, as *supra*, it is noted that the specification has not even provided teachings to show the phenotype of the transgenic mice that were produced.

Additionally, as the claimed invention broadly reads on any transgenic mammals, it is reiterated that the specification fails to provide an enabling disclosure for the preparation of any transgenic animals harboring any mutant GPIIIa gene, because the guidance offered in the specification is not sufficient to teach one skilled in the art as to how to prepare the claimed transgenic animals exhibiting an appropriate phenotype. Since homologous recombination is required for the gene targeting methods, such as those employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out this method. It is reiterated that the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species [see prior Office action, pp. 10-11].

The specification discloses no phenotype for the claimed transgenic animals, other than the anticipated expression of the transgene. Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover the use of any species of transgenic mammal in methods of comparing platelet function and methods of screening, but the specification does not enable this use. In the absence of disclosure of a transgenic animal exhibiting the appropriate phenotype, undue experimentation would have been required to make and/or use the claimed transgenic non-human mammals and methods of using the same.

Accordingly, in view of the quantity of experimentation necessary for the production and methods of use of any non-human mammal and methods of making a non-human mammal expressing a transgene stably introduced into its DNA, wherein the transgene comprises a mutant GP IIIa where at least one or more phosphorylable cytoplasmic domain tyrosine residues has been replaced with a non-tyrosine residue and methods of using the same, the unpredictable and undeveloped state of the transgenic and ES art, and particularly with respect to the unpredictable nature of the phenotypic effect, it would have required undue experimentation for one skilled in the art to make and/or use the claimed transgenic non-human mammals and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27, 30-34, 51-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites the limitation "said phosphorylatable" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claims 30 and 32 recite the limitation "phosphorylatable cytoplasmic domain tyrosine residues" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claim. Claims 31-34 depend on claim 30.

Claim 51 is drawn to methods, but no clear and defined steps are recited in the independent claims. In particular, it is unclear how "comparing" one or more biological responses between a transgenic and non-transgenic non-human mammal of the same species, relates to determining mutant GP IIIa protein modulation. It is unclear what "biological" response is being compared to show mutant GP IIIa protein modulation. Claims 52-66 depend on claim 51.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

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